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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/666,267 | 09/21/2000 | Peter S. Linsley | 30436.11US06 | 1523 |

7590 04/22/2002

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| EXAMINER |
|---|
| GAMBEL, PHILLIP |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | 8 |

DATE MAILED: 04/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Applicati n N . | Applicant(s) |
|---|---|---|
| | 09/666267 | LINSLEY ETAL. |
| | Examin r | Art Unit |
| | GAMBEL | 1644 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☑ Claim(s) _____ is/are pending in the application. 77-88

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 77-86

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 87-88

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 9/21/00 is/are: a)☐ accepted or b)☑ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)
2) ☑ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

1. Applicant's election with traverse of Group II (claims 87-88) in Paper No. 6 is acknowledged. The traversal is on the ground(s) that it would not be undue burden. This is not found persuasive because of the reasons of record set forth in the Restriction (Paper No. 5). MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required. Regarding applicant's comments about undue burden, the MPEP 803 (July 1998) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that examination Groups require non-coextensive searches. The Inventions are distinct for reasons elaborated in the previous Office Action.

The requirement is still deemed proper and is therefore made FINAL.

Claims 77-86 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-76 have been canceled previously.

2. The filing date of the instant claims as they read on methods of producing antibodies to B7 (see rejections under 35 USC 112, first paragraph, below) is deemed to be the filing date of the priority application USSN 07/722,101, filed 6/27/91, as the previous priority applications do not appear to provide sufficient written description for the claimed methods of producing antibodies.

If applicants disagree, applicants should present a detailed analysis as to why the claimed subject matter has clear support in the parent application. Applicant is invited to verify the priority date of the instant claims, including written support and enablement under 35 USC 112, first paragraph.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

5. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, no CRF appears to have been filed. Therefore, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

The following procedure is to be used for cases that contain the same sequence disclosure as the parent application. The applicant need not submit a new computer readable from of the Sequence Listing in this asserted divisional application. However, (1) the specification must contain a paper copy of the Sequence Listing, (2) applicant must request in writing that the CRF in the parent case be used to prepare a file for the offspring and (3) applicant must submit a statement that the paper copy of the Sequence Listing in the offspring is identical to the computer readable form submitted in the parent case.

Applicant is invited to clarify what date of priority applicant asserts for the Sequence Listing and whether the instant application is a divisional or continuation-in-part of parent application USSN 08/219,200..

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. This is a rejection under 35 USC § 112, first paragraph, new matter.

Claims 87-88 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed:

Claim 87. A method for generating and identifying antibodies for a B7 antigen that inhibit B cells from binding CD28 comprising:

(a) screening a sample of B cells that bind CD28;
(b) isolating and purifying proteins mediating the B cell binding with CD28;
(c) immunizing an animal with an antigenic portion of the purified proteins;
(d) harvesting antibodies so produced; and
(e) screening the antibodies for antibodies that inhibit CD28 binding to B cells.

The method of claim 87, wherein the antibodies inhibit CD28 binding to B cells by at least approximately 30%.

Applicant's amendment, filed 12/27/00 (Paper No. 3), directs support to pages 18-28, 35, 38 and Figure 4 for the written description for the above-mentioned "limitations"

In contrast to applicant's reliance on pages 18-28, 35, 38 and Figure 4 for the written description for the above-mentioned "limitations"; the instant specification as filed appears to provide for methods of producing monoclonal antibodies reactive with B7Ig fusion proteins according to the standard Kohler-Milstein method wherein the antibodies are screened for the desired specificity with B7Ig fusion protein that has been used for immunization (see page 19, paragraphs 1-3 of the instant specification) and isolating antibodies according to conventional methods (see page 20, paragraph 1 of the instant specification) or may be used to react with B7 antigen positive cells such as B cells to inhibit B cell interaction via the B7 antigen with CD28 positive T cells (see page 23, paragraph 1 of the instant specification).

Page 38, paragraph 1 of the specification provides for characterization of a panel of monoclonal antibodies to B cell surface antigens and the characterization of the particular BB-1 antibody that could block CD28-mediated adhesion by greater than 30%.

In contrast to applicant's reliance, the specification as filed does not provide sufficient written description for the particular steps Claim 87 (a) - (e) and Claim 88, as currently recited. For example, the disclosed method of making antibodies are directed towards methods of employing the B7Ig fusion protein as immunogen and not screening " samples of B cells that bind CD28", "isolating and purifying proteins mediating the B cell binding with CD28" and "immunizing an animal with an antigenic portion of the purified proteins". The specification as filed discloses that the resultant antibodies are screened for binding to the B7Ig that has been used for immunization or react with B7 antigen positive cells such as B cells to inhibit B cell interaction via the B7 antigen with CD28 positive T cells and not for "screening the antibodies for antibodies that inhibit CD28 binding to B cells". Furthermore, the specification as discloses the characterization of a particular BB-1 antibody and with a given property of blocking CD28-mediated adhesion by greater than 30% and not for a screening method for antibodies inhibit CD28 binding to B cells by at least approximately 30%.

Given the written description in the specification as filed, applicant should recite "producing antibodies" rather than "method for generating and identifying antibodies for a B7 antigen".

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed.

It appears that the claimed methods do not have written description in the specification as filed; therefore the claims represent a departure from the specification and claims as originally filed. Applicant's reliance on generic disclosure and possibly a single or limited species do/does not provide sufficient direction and guidance to the "features" currently claimed. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06.

10. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 87-88 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing "a B7 antigen" "antigenic portion of the purified proteins" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of both the "B7 antigen" and the "antigenic portion of the purified proteins", are not set forth in the specification as filed, commensurate in scope with the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The instant specification only discloses that the B7 antigen was isolated and disclosed by Freeman et al. (J. Immunol. 143: 2714 -2722, 1989) (1449), that the B7Ig fusion proteins was deposited with ATCC as Accession Number 68627, and that the B7 antigen is the B-7/BB-1 antigen. See page 11, paragraphs 1 and 2 and page 13, paragraph 1 of the instant specification.

Applicant is relying upon certain biological activities and the disclosure of this limited representative number of species to support an entire genus. The instant invention encompasses producing antibodies to any "B7 antigen" and employing any "antigenic fragment of any B7 antigen", yet the instant specification does not provide sufficient written description as to the structural features of said "B7 antigens and fragments" as currently encompassed by the claims. Also, the specification does not provide for the correlation between the chemical structure and the function of the genus of "B7 antigens and fragments", currently encompassed by the claimed invention. The reliance on the disclosed limited examples of the "B7/BB-1" or "B7Ig" indicated above and disclosed in the specification as filed does not support the written description of any "B7 antigen or antigenic fragment thereof. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities. The specification as filed does not provide written description for B7 molecules structurally unrelated to the "B7/BB-1" or "B7Ig" indicated above and disclosed in the specification as filed and encompassed by the claimed invention.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying a "B7 antigen or antigenic fragment" structurally unrelated to the "B7/BB-1" or "B7Ig" indicated above and disclosed in the specification as filed

There is insufficient guidance based on the reliance on the "B7/BB-1" or "B7Ig" indicated above and disclosed in the specification as filed to direct a person of skill in the art to select or to predict particular sequences as essential for identifying any "B7 antigen or antigenic fragment" nor what other "B7 antigens" are composed of, as encompassed by the claimed invention.

For example, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

With respect to applicant's priority, it is noted that Linsley et al. (PNAS 87: 5031-5035, 1990) (1449) discloses that homologs of CD28 and B7/BB-1 have not yet been identified in other mammalian species (see page 5035, column 1, last sentence).

The specification does not disclose nor identify "B7 antigens" other than the B7 antigen which was isolated and disclosed by Freeman et al. (J. Immunol. 143: 2714 -2722, 1989) (1449) or the B7Ig fusion protein which was deposited with ATCC as Accession Number 68627). See page 11, paragraphs 1 and 2 and page 13, paragraph 1 of the instant specification.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "B7 antigens", the specification does not provide sufficient written description for the genus of "B7 antigens or antigenic fragments currently claimed".

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "B7 antigens or antigenic fragments"; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

11. Claims 87-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "the B7 antigen set forth in Freeman et al. J. Immunol. 143: 2714-2722, (1989), as disclosed on page 11, paragraphs 1-2 of the instant specification or the B7Ig fusion protein deposited with ATCC as Accession Number 68627, as disclosed on page 13, paragraph 1 of the instant specification, does not reasonably provide enablement for any "B7 antigen or antigenic fragment" to be the specificity or to be employed as an immunogen in the instant claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims. molecule

The instant specification only discloses that the B7 antigen was isolated and disclosed by Freeman et al. (J. Immunol. 143: 2714 -2722, 1989), that the B7Ig fusion proteins was deposited with ATCC as Accession Number 68627, and that the B7 antigen is the B-7/BB-1 antigen. See page 11, paragraphs 1 and 2 and page 13, paragraph 1 of the instant specification.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the "B7 antigen or antigenic fragment" as the immunogen or target specificity of the claimed methods. B7 may have some notion of the source of the antigen, however, claiming biochemical molecules by a particular name given to the protein (e.g B7 antigen) by various workers in the field fails to distinctly claim what that protein is and what it is made up of. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "B7 antigen or antigenic fragment thereof".

For example, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

With respect to applicant's priority, it is noted that Linsley et al. (PNAS 87: 5031-5035, 1990) discloses that homologs of CD28 and B7/BB-1 have not yet been identified in other mammalian species (see page 5035, column 1, last sentence).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any "B7 antigen or antigenic fragment thereof", yet the instant specification does not provide sufficient guidance and direction as to the structural features of said "B7 antigens and antigen fragments" broadly encompassed by the claimed invention and the correlation between the chemical structure of B7 disclosed in the specification as filed to the genus of B7 antigens, encompassed by the claimed invention. The reliance on the disclosed limited example(s) of B7 disclosed by Freeman et al. (J. Immunol. 143: 2714 -2722, 1989) or of the B7Ig fusion proteins deposited with ATCC as Accession Number 68627 (see page 11, paragraphs 1 and 2 and page 13, paragraph 1 of the instant specification) does not support the scope of enablement for any "B7 antigen or antigenic fragment".

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands. Therefore, structurally unrelated or divergent B7 molecules or antigens encompassed by the claimed invention other than the B7 disclosed by Freeman et al. (J. Immunol. 143: 2714 -2722, 1989) or the B7Ig fusion proteins deposited with ATCC as Accession Number 68627 would be expected to have differences in their physicochemical properties or functional activities.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "B7 antigens or antigenic fragments" other than the B7 or B7Ig disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of ligand and receptors encompassed by the claimed invention.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "B7 antigens or antigenic fragments" other than the B7 or B7Ig disclosed in the specification as filed as the target specificity or immunogen in the claimed methods

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using "B7 antigens or antigenic fragments" other than the B7 or B7Ig disclosed in the specification as filed as the target specificity or immunogen in the claimed methods would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

12. As pointed out in the priority application USSN 08/459,766 and the issues set forth herein, applicant should provide sequence information for the essential subject matter of the B7 disclosed in the specification as filed and claimed.

However, applicant has not provided the sequence of the B7 antigen of the claimed invention as isolated and disclosed by Freeman et al. (J. Immunol. 143: 2714 -2722, 1989) or the B7Ig fusion protein which was deposited with ATCC as Accession Number 68627. See page 11, paragraphs 1 and 2 and page 13, paragraph 1 of the instant specification.

The current Sequence Listing does not provide the amino acid sequence of the B7 antigen, as defined by Freeman et al. (J. Immunol. 143: 2714-2722, 1989).

The amino acid sequence is considered essential subject matter to the instant application and the claimed invention.

Applicant is reminded to provide said Sequence Listing which complies with the requirements of 37 CFR 1.821 through 1.825 for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded to provide the appropriate Hawkins Declaration to accompany amending the instant specification to provide the essential subject of the amino acid sequence defining the claimed B7 antigen, as set forth by Freeman et al. (J. Immunol. 143: 2714-2722, 1989).

The following is noted.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

Alternatively, applicant may satisfy the claimed B7 antigen by satisfying the deposit of biological materials under 35 USC 112, first paragraph by depositing the B7Ig fusion protein which was deposited with ATCC as Accession Number 68627. In this case, it would be apparent that ATCC Accession Number 68627 deposit would be required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent plasmid or vector or cell lines which produce these antibodies. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

Applicant is reminded that the following and should amend the specification accordingly.
The current address of the ATCC is as follows:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

13. Claims 87-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing monoclonal antibodies reactive with B7Ig fusion proteins according to the standard Kohler-Milstein method wherein the antibodies are screened for the desired specificity with B7Ig fusion protein that has been used for immunization (see page 19, paragraphs 1-3 of the instant specification) and isolating antibodies according to conventional methods (see page 20, paragraph 1 of the instant specification) or may be used to react with B7 antigen positive cells such as B cells to inhibit B cell interaction via the B7 antigen with CD28 positive T cells (see page 23, paragraph 1 of the instant specification) does not reasonably provide enablement for any method for producing antibodies to B7, including the particular steps Claim 87 (a) - (e) and Claim 88, as currently recited.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims. molecule

As pointed out above, the specification as filed provides for producing antibodies to B7 using the B7Ig fusion protein

As pointed out above and in contrast to applicant's reliance on pages 18-28, 35, 38 and Figure 4 for the written description for the particular steps Claim 87 (a) - (e) and Claim 88, as currently recited; the instant specification as filed appears to provide for methods of producing monoclonal antibodies reactive with B7Ig fusion proteins according to the standard Kohler-Milstein method wherein the antibodies are screened for the desired specificity with B7Ig fusion protein that has been used for immunization (see page 19, paragraphs 1-3 of the instant specification) and isolating antibodies according to conventional methods (see page 20, paragraph 1 of the instant specification) or may be used to react with B7 antigen positive cells such as B cells to inhibit B cell interaction via the B7 antigen with CD28 positive T cells (see page 23, paragraph 1 of the instant specification).

Applicant has not provided sufficient guidance and direction to other methods of producing antibodies to B7 antigen, other than that indicated in the previous paragraph.

Applicant is invited to provide clear and distinct method steps and ingredients, which are supported by the written description of the specification as filed.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06. Applicant should not use the phrase "Kohler-Milstein" in the claims.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 87-88 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ledbetter et al. (U.S. Patent No. 5,182,368) in view of Linsley et al. (PNAS 87: 5031-5015, 1991) (1449) and Freeman et al. (J. Immunol. 143: 2714-2722, 1989) (1449).

Ledbetter et al. teach the standard methods of making antibodies to antigens expressed by and isolated from lymphocytes (e.g. B cells) at the time the invention was made (see entire document, particularly the Detailed Description of the Invention). Ledbetter et al. teach the art known and practiced procedures of isolating and screening for antigens of interest, the use of the standard Kohler-Milstein method of producing monoclonal antibodies to antigens of interest and screening for the desired activity of said antigens of interest.

Ledbetter et al. differs from the claimed methods by not disclosing B7 as the antigen of interest.

Linsley et al. teach that the T cell activation antigen CD28 mediates adhesion with B cells by interaction with the activation antigen B7/BB-1, including that the monoclonal BB-1 antibody which binds the B cell activation antigen B7 and blocks the CD28-mediated adhesion (see entire document, including the Abstract, pages 5033-5034 and the Discussion).

Linsley et al. also teach that Freeman et al. (J. Immunol. 143: 2714-2722, 1989) disclose B cell antigen and confers specificity to CD28 (see page 5034).

Linsley et al. teach that CD28-mediated adhesion is important for T helper cell regulation of antigen-specific B lymphocyte responses (see Discussion).

Freeman et al. teach the expression, isolation and cloning of the B7 antigen expressed on activated and neoplastic B cells (see entire document).

Given the expression of B7 on activated and neoplastic B cells and the role of B7 in CD28-mediated adhesion, one of ordinary skill in the art at the time the invention was made would have been motivated to screen and isolate B7 from B7 expressing cells, as taught by Linsley et al. and Freeman et al. and to generate monoclonal antibodies to B7 by standard antibody technology at the time the invention was made, as taught by Ledbetter et al., by screening for specificity to B7 or B7 expressing cells and the ability to inhibit CD28:B7 interactions. The use of mononclonal antibodies in various purification and immunoassays as well as determining structure-function relationships of antigens of interest was well known and practiced at the time the invention was made by the ordinary artisan. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

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Technology Center 1600
April 22, 2002